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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/246,451	02/09/1999	FRANCES H. ARNOLD	93731E827US1	6181

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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/246,451	ARNOLD ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *146-173,175-177,179-181,183-185 and 187-189* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *160* is/are allowed.

6)☒ Claim(s) *146-159,161-173,175-177,179-181,183-185 and 187-189* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 146-173, 175-177, 179-181, 183-185, 187-189 are currently pending in this application.

Applicants' amendments and arguments filed on 8-20-02, paper No. 18, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 146-159, 161-173, 175-177, 179-181, 183-185, 187-189 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a functional cytochrome P450 oxygenase variants having at least 2 to about 10 times the catalytic activity and stability of wild type cytochrome P450 oxygenase from P.putida and comprising mutations at positions 331, 280, 242 (either individually or in combination) of SEQ ID NO:2, does not reasonably provide enablement for any such variant cytochrome P450 oxygenase comprising above specific mutations and a 90% amino acid sequence identity to SEQ ID NO: 2 or a functional variant of the above enzyme encoded by a first polynucleotide that hybridizes to a second polynucleotide under conditions of high stringency, wherein the second polynucleotide

encodes the cytochrome P450 oxygenase variant enzyme comprising the three above specific mutations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 149-159 and 161-189 are so broad as to encompass any variant cytochrome P450 enzyme comprising the mutations at positions and a 90% amino acid sequence identity to SEQ ID NO: 2 or a functional variant of the above enzyme encoded by a first polynucleotide that hybridizes to a second polynucleotide under conditions of high stringency, wherein the second polynucleotide encodes the cytochrome P450 oxygenase variant enzyme comprising the three above specific mutations. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of variant oxygenases broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence, and obtain the desired activity, requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed

knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only three specific variants. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides which have the above specific mutations and a 90% amino acid sequence identity to SEQ ID NO: 2 or a functional variant of the above enzyme encoded by a first polynucleotide that hybridizes to a second polynucleotide under conditions of high stringency, wherein the second polynucleotide encodes the cytochrome P450 oxygenase variant enzyme comprising the three above specific mutations. The specification is limited to teaching use of SEQ ID NO:2 with the above specific mutations as an oxygenase with improved properties when compared to the wild type enzyme but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any

protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any cytochrome P450 oxygenase with 90% identity to the enzymes of SEQ ID NOS:2 because the specification does not establish: (A) regions of the protein structure which may be modified without effecting the activity; (B) the general tolerance of cytochrome P450 oxygenases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue in any cytochrome P450 oxygenase with an expectation of obtaining the desired improved biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including cytochrome P450 oxygenases with an enormous number of amino acid modifications of the cytochrome P450 oxygenase with SEQ ID NO:2. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of variant cytochrome P450 oxygenases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

Claim 160 is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

MANJUNATH RAO
PATENT EXAMINER

Manjunath N. Rao Ph.D.
6/5/03